



**University of
Zurich^{UZH}**

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2008

A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up

Szeimies, R M ; Ibbotson, S ; Murrell, D F ; Rubel, D ; Frambach, Y ; de Berker, D ; Dummer, R ; Kerrouche, N ; Villemagne, H

Abstract: **OBJECTIVE:** To compare the efficacy and cosmetic outcome (CO) of photodynamic therapy with topical methyl aminolevulinate (MAL-PDT) with simple excision surgery for superficial basal cell carcinoma (sBCC) over a 1-year period. **METHODS:** In this multicentre, randomised, controlled, open study, patients were treated at baseline either with MAL-PDT (two sessions, 7 days apart, repeated 3 months later if incomplete clinical response) or surgery (at baseline). Primary endpoints were clinical lesion response (CR) 3 months after last treatment and CO assessed by the investigator 12 months after last treatment. Secondary endpoints were CR at 12 months (i.e. recurrence) and CO assessed by the investigator at 3 and 6 months and by the patient at 3, 6 and 12 months. **RESULTS:** Overall, 196 patients were enrolled with 1.4 sBCC lesions on average per patient. Mean lesion count reduction at 3 months was 92.2% with MAL-PDT vs. 99.2% with surgery [per protocol (PP) population] confirming the non-inferiority hypothesis (95% confidence interval, -12.1, -1.9). A total of 92.2% lesions showed CR at 3 months with MAL-PDT vs. 99.2% with surgery (PP population). At 12 months, 9.3% lesions recurred with MAL-PDT and none with surgery. CO was statistically superior for MAL-PDT at all time points. At 12 months, 94.1% lesions treated with MAL-PDT had an excellent or good CO according to the investigator compared with 59.8% with surgery. This difference was confirmed with the patients' assessment. The proportion of excellent CO markedly improved with time with MAL-PDT unlike surgery. **CONCLUSIONS:** MAL-PDT offers a similarly high efficacy and a much better CO than simple excision surgery in the treatment of sBCC.

DOI: <https://doi.org/10.1111/j.1468-3083.2008.02803.x>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-13908>

Journal Article

Accepted Version

Originally published at:

Szeimies, R M; Ibbotson, S; Murrell, D F; Rubel, D; Frambach, Y; de Berker, D; Dummer, R; Kerrouche, N; Villemagne, H (2008). A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. *Journal of the European Academy of Dermatology and Venereology*, 22(11):1302-1311.

DOI: <https://doi.org/10.1111/j.1468-3083.2008.02803.x>

A clinical study comparing Methyl Aminolevulinate Photodynamic Therapy (MAL-PDT) and Surgery in superficial Basal Cell Carcinoma, with a 12-month follow-up.

Authors

R.M. Szeimies¹, D. de Berker², R. Dummer³, S. Ibbotson⁴, D.F. Murrell⁵, D. Rubel⁶, Y.
Frambach⁷, N. Kerrouche⁸, H. Villemagne⁸ on behalf of the *Excilight Study* Group

Institutions

¹Klinikum der Universität, Regensburg, Germany – ²Bristol Royal Infirmary, Bristol, United
Kingdom – ³Universitätsspital, Zürich, Switzerland - ⁴Ninewells Hospital, Dundee, Scotland,
UK - ⁵St George Hospital and University of NSW, Sydney, Australia - ⁶Skin and Cancer
Foundation, Darlinghurst, Australia - ⁷ Universität zu Lübeck, Klinik für Dermatologie, Lübeck,
Germany - ⁸Galderma Medical and Marketing, Sophia Antipolis, France

Author for correspondence

Rolf Markus Szeimies

Klinikum der Universität - Hautklinik

Franz Josef Allee 11

93053 Regensburg

Tel.: +49 941 944 96 14

Fax.: +49 941 944 9611

rolf-markus.szeimies@klinik.uni-regensburg.de

Funding Sources

This study was funded by Galderma R&D, Sophia Antipolis, France.

Conflict of interest statement

The investigating authors received payments for this research project. Two of the authors are employees of Galderma R&D (H. Villemagne and N. Kerrouche).

Reprint Requests

Herve Villemagne, Galderma Research & Development, 2400 route des Colles, BP 87, 06902 Sophia Antipolis Cedex, France. herve.villemagne@galderma.com

Word Count: Abstract = 366 words; Text = 3811 words.

References: 28

Tables: 4

Figures: 9

ABSTRACT (No length limit fixed by JEADV)

BACKGROUND: In recent years, photodynamic therapy (PDT) has gained increasing interest in the treatment of skin cancers and is competing with standard therapeutic strategies.

OBJECTIVE: The objective of this study was to compare the efficacy and cosmetic outcome of PDT with methyl aminolevulinate (MAL-PDT) with simple excision surgery for superficial BCC (sBCC) over a one year period.

METHODS: This was a prospective, multicentre, randomised, controlled, open study. Patients were treated at baseline either with MAL-PDT (2 treatment sessions 7 days apart, repeated 3 months later for lesions with incomplete clinical response) or elliptical excision surgery with 3mm margin (at baseline). Primary endpoints were clinical lesion response 3 months after last treatment and cosmetic outcome assessed by the investigator 12 months after last treatment. Secondary endpoints were clinical lesion response at 12 months (i.e. recurrence), cosmetic outcome assessed by the investigator at 3 and 6 months and by the patient at 3, 6 and 12 months after last treatment.

RESULTS: A total of 196 patients were randomised in a 1:1 ratio to MAL-PDT or surgery, with 1.4 sBCC lesions on average per patient. Mean lesion count reduction 3 months after last treatment was 92.2% with MAL-PDT versus 99.2% with surgery (PP population) confirming the non inferiority of MAL-PDT compared to surgery (95%CI [-12.1;-1.9]). In terms of lesion response, 118/128 lesions (92.2%) showed complete clinical response at 3 months with MAL-PDT versus 117/118 (99.2%) with surgery (PP population). At 12 months, 11/118 lesions (9.3%) recurred with MAL-PDT and none with surgery. Cosmetic outcome, whether assessed by the investigator or by the patient, was statistically superior for MAL-PDT at all time points. Twelve months after last treatment, 96/102 lesions (94.1%) treated with MAL-PDT had an excellent or good cosmetic outcome as judged by the investigator compared with 70/117 (59.8%) with surgery. When assessed by the patients, this remained in favour of MAL-PDT compared to surgery (98/100 [98.0%] and 95/115 [82.6%], respectively). The proportion of excellent cosmetic outcome markedly improved with time in the MAL-PDT group whereas it remained almost unchanged in the surgery group.

CONCLUSIONS: MAL-PDT offers the advantage of a similarly high efficacy and a much better cosmetic outcome than simple excision surgery in the treatment of sBCC.

Key words: methyl aminolevulinate, photodynamic therapy, superficial basal cell carcinoma, recurrence, cosmetic outcome, surgery.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignant neoplasm in fair-skinned people in Western industrialized countries. It comprises approximately 70 to 80% of all skin cancers in North America¹. BCC is classified together with squamous cell carcinoma (SCC) as nonmelanoma skin cancer (NMSC). NMSC affects 1-2% of the population annually.^{2,3} In the USA, 0.9-1.2 million estimated new cases of NMSC are diagnosed each year and of these 80% are BCC². In Australia, depending on the regions, the incidence ranges from 729 per 100,000 individuals to twice this figure.³

In Europe, published data report incidence of NMSC to be higher in the Northern countries than in the Mediterranean area with figures ranging from 24/11 (males/females) per 100,000 in Spain to 153/114 in the United Kingdom.⁴

BCCs can be divided into three major groups, superficial, nodular and infiltrating morpheaform lesions. They rarely metastasize but can induce significant local tissue destruction and disfigurement. Nodular BCCs (nBCC) account for 60% of all BCCs and superficial BCCs (sBCC) account for most of the remainder. sBCCs are slow growing cancers, occurring mostly on the trunk in men, and on the head or legs in women.^{5,6,7,8} It has been suggested that intermittent sun exposure may be an etiologic factor in superficial BCC as compared with chronic sun exposure in nodular BCC.⁷ However, so far, this has not been clearly established⁹.

Current modalities in the treatment of BCC include surgical techniques (surgical excision, curettage and electrodesiccation, Mohs micrographic surgery, and cryosurgery), nonsurgical interventions (photodynamic therapy, radiotherapy) and pharmacologic treatments (topical 5-fluorouracil and imiquimod).^{10,11} The treatment used depends on the type, size, depth and localisation of the BCC lesion.

For the treatment of superficial BCC, surgical excision surgery is generally regarded as the treatment of choice. However, one disadvantage of surgical excision is lack of precision in margin control. Indeed, in order to avoid incomplete excision, removal of normal tissue

Kommentar [Zeina1]:
Although this is not in agreement with Telfer guidelines (BJD, 1999), this is stated in most articles.

surrounding the tumour margins is needed.¹¹² Such a technique needs to be performed by an experienced dermatologist or by a surgeon.

In addition, a relationship between incomplete excision of tumor margins and recurrence risk was demonstrated^{11,12,13} adding further to surgery issues.

Recently, there has been an increased interest in the use of topical photodynamic therapy (PDT) for the treatment of skin cancer¹⁴. PDT is a non-invasive treatment option which involves two major steps: (i) preferential absorption and accumulation of photodynamically active porphyrins in neoplastic tissue; and (ii) illumination with a specific light source leading to the release of reactive oxygen species within the target tissue.¹⁵ The subsequent destruction of the targeted cells occurs by apoptosis or necrosis.

In the treatment of NMSC, topical PDT has the advantage of being limited to the application site and illumination field. More importantly, the photosensitizer is preferentially retained in the tumour tissue. The selectivity depends on the photosensitizing agent used. As there are no cumulative toxic effects, such as with radiation therapy, treatment can be repeated.

PDT with topical methyl aminolevulinate (MAL-PDT) has been approved in Europe, Australia and New Zealand for the treatment of actinic keratoses, BCCs (nodular and superficial) and, in some countries, for Bowen's disease. Numerous published studies have shown the benefit of MAL-PDT in terms of efficacy, safety, cosmetic outcome and patient satisfaction in these indications.¹⁶⁻²⁴

One study in particular has been performed comparing MAL-PDT to surgery in patients with nodular BCC.¹⁹ This study showed an excellent cure rate for MAL-PDT, comparable to surgery (respectively 92% and 98% of patients with clinical complete response rate at three months after last treatment), and a superior cosmetic outcome for MAL-PDT. However, a trend for higher recurrence rate was observed at 24 months with MAL-PDT.

In another study, comparing MAL-PDT to cryotherapy for the treatment of superficial BCC,²⁴ MAL-PDT proved as effective as double freeze-thaw cryotherapy, with lesion complete response rate of 97% for MAL-PDT vs 95% for cryotherapy three months after last treatment.

Long term efficacy was also demonstrated with cumulative recurrence rates of 22% for MAL-PDT versus 20% for cryotherapy at the end of a five-year follow-up period. At that time, notably more patients had excellent cosmetic outcome with MAL-PDT (56%) than with cryotherapy (14%).

However, no comparison was made between MAL-PDT and the gold standard, surgery, in the treatment of superficial BCC. The aim of this prospective, multicentre, randomized, controlled, parallel-group, open study was to compare the efficacy, safety, and cosmetic outcome of MAL-PDT with simple excision surgery for the treatment of superficial BCC over a one-year period.

METHODS

Study design

The study was performed in accordance with Good Clinical Practices and in compliance with local regulatory requirements. The appropriate national authorities and local Ethics Committees approved the protocol before study commencement. All patients provided written informed consent before inclusion into the study.

This was a multicentre, controlled, randomized, open, parallel-group clinical trial performed between August 2004 and November 2006. Twenty seven (27) investigator centres participated in the study: 10 in the United Kingdom, 10 in Germany, 2 in Switzerland and 5 in Australia.

The objectives of the study were to show a non-inferior efficacy of MAL-PDT compared to surgery in terms of lesion response 3 months after last treatment, and a superiority of MAL-PDT over surgery in terms of cosmetic outcome 12 months after last treatment.

Kommentar [Zeina2]: This is the only part of the article where the objectives of the study are precisely stated. Therefore, I left this paragraph as it was.

Patients

Eligible patients were males or females older than 18 years with a clinical diagnosis of primary superficial BCC, suitable for simple excision surgery, confirmed by histology and with no histological evidence of aggressive growth patterns. Excluded from the study were patients with more than five eligible lesions; lesions located in the mid-face region (nose, nasolabial or orbital areas); lesions with a largest diameter less than 8 mm or more than 20 mm; recurrent lesions; lesions located in severely sun-damaged skin where surgery was not suitable due to frequent recurrence/occurrence of other BCCs in the same area; lesions located close to or involving a scar of Squamous Cell Carcinoma; pigmented, morpheaform or infiltrating lesions on the treated area. Patients who were at risk in terms of precautions, warnings, and contraindications as indicated in the package insert for MAL-PDT as well as women who were pregnant or breastfeeding were excluded. Concurrent use on the study treatment areas of cryotherapy, surgery, 5 fluorouracil, radiotherapy, aminolevulinate based photodynamic therapy (ALA-PDT), imiquimod, electrodesiccation or curettage was prohibited.

Treatments

At screening, a biopsy was performed for histological confirmation of the lesions. Biopsy was not required if a histological report dated from less than 6 months was available.

Within four weeks of the screening visit, eligible patients were randomised consecutively to MAL-PDT or excision surgery. Treatment assignment was done at each investigator site: at study initiation, a block of numbered randomisation cards was provided to each site; whenever a patient was considered eligible, the investigator had to scratch a randomization card, following an ascending number order, to disclose the procedure assigned to the patient. The date and time of disclosure were documented to ensure randomisation order was respected.

Patients randomised to MAL-PDT were treated with one cycle of 2 treatment sessions 7 days apart. sBCC lesions showing non complete response 3 months later could be retreated with a second cycle of 2 MAL-PDT sessions 7 days apart. Prior to each PDT session, if deemed necessary, the sBCC lesions were prepared, without bleeding or pain, to remove scales and crusts and roughen lesion surface. Then, a layer of about 1mm thick of MAL 160mg/g cream

(Metvix[®], Galderma SA, Lausanne, Switzerland – PhotoCure ASA, Oslo, Norway) was applied to the lesion and the surrounding 5-10mm of normal skin. The treated area was covered with an occlusive dressing for 3 hours then washed off with saline solution. Subsequently, lesions were exposed to red light using a large-field LED light source (Aklite[™] CL 128 or CL 16, Galderma SA, Lausanne, Switzerland – PhotoCure ASA, Oslo, Norway) during 7 to 10 minutes to deliver a total dose of 37 J/cm². Mini desk fans were provided to the centres to cool the irradiation sites during red light exposure.

For patients randomised to surgery, one simple elliptical excision surgery was performed at baseline according to the investigators routine practice with a 3-mm margin from the clinically estimated edge of the lesion. The excised specimen was sent for histological examination.

There was a 12-month follow-up period after last treatment procedure in both groups. Therefore, the duration of the study for each patient was 13 to 16 months depending on whether one or two MAL-PDT cycles were required. For patients who received one MAL-PDT cycle and for those who underwent surgery, study visits took place at screening, baseline, Week 1, Week 13, Month 6 and Month 12, and a safety follow-up phone call was given at Week 3. For patients who required two MAL-PDT cycles, additional visits took place at Week 14, Month 9 and Month 15, and a phone call was scheduled at Week 15.

Lesions showing an incomplete clinical response 3 months after last treatment were not assessed during the subsequent visits and it was the responsibility of the investigator to consider the best alternative therapy.

Outcome measures

For the sake of simplification, results '3, 6 and 12 months after last treatment' are stated hereafter as results 'at 3, 6 and 12 months'.

The primary outcomes were the clinical lesion response at 3 months [complete response (CR): complete clearance of the lesion, non complete response (non CR): non complete

clearance of the lesion], and the cosmetic outcome assessed by the investigator at 12 months on a 4-point scale (0: poor, 1: fair, 2: good, 3: excellent).

The secondary outcomes were: lesion recurrence at 12 months; cosmetic outcome assessed by the investigator at 3 and 6 months; cosmetic outcome assessed by the patient at 3, 6 and 12 months on the same 4-point scale as above.

Adverse events, whether reported spontaneously by the patient or elicited following non-leading questioning, were recorded at each visit together with their severity, duration and need for additional therapy. Investigators were asked to list under *photosensitivity reaction* expected reactions such as skin discomfort, burning sensation, erythema, stinging, among others, reported with MAL-PDT.

Kommentar [Zeina3]: This sentence was initially included in the Results - Adverse Events section

Statistical methods

Based on published data on the efficacy of simple excision surgery in nodular BCC¹⁹, it was assumed that in the present study, this modality would lead to a 90% reduction in lesion count and that the response to MAL-PDT would be the same. The largest clinically acceptable difference in terms of percent reduction in lesion count 3 month after the last treatment was 15%. If the lower limit of the confidence interval of the difference (MAL-PDT – simple excision surgery) was above -15%, MAL-PDT was considered non-inferior to simple excision surgery. In terms of cosmetic outcome, based on the results of the same published study, it was decided to set a 40% minimal difference in favour of MAL-PDT over simple excision surgery. If the p-value was below 0.05 and the difference positive, then MAL-PDT was declared superior to simple excision surgery.

Kommentar [Zeina4]: I confirm there's no other published study comparing MAL-PDT with surgery

With an assumed 90% reduction in lesion count with simple excision surgery, a two-sided 95% confidence interval for the difference between groups, an alpha risk set at 5% two sided and a power of approximately 90%, it was calculated that 84 patients would be necessary per group. With this number of patients the power would be around 99% for the cosmetic outcome, and the overall power on this study (intersection of the two alternative hypotheses) would be around 90% on this trial. Assuming a 15% rate of non-evaluable patients, a total of 198 patients needed to be enrolled (99 patients in each group).

To analyse the lesion response, the percent reduction in lesion count per patient was calculated to compare both treatments. The percent reduction in lesion count was submitted to a weighted analysis of variance including treatment effect. The analysis of variance was weighted by number of treated lesions per patient at baseline. The 95% Confidence Interval was calculated from the weighted analysis of variance on the *per protocol* (PP) population. Intent-To-Treat (ITT) analysis using the Worst Case scenario (all missing values were considered as Non Complete Response) was also performed to assess the robustness of the results obtained on the PP population. Additionally, the lesion response rate (Complete Response/Non Complete Response) 3 months after the last treatment and the recurrence rate after 12-month follow-up were descriptively presented by treatment.

To analyse the Cosmetic outcome, a success/failure rate (dichotomous variable) was calculated to compare both treatments. Success per patient was defined as a mean across lesions scored greater or equal to 2 (at least good cosmetic outcome). The superiority of MAL-PDT over simple excision surgery was demonstrated by showing a significant difference between these two groups for the success/failure rate using a Cochran-Mantel-Haenszel test (CMH) stratified by centre with the rdit transformation and the row mean scores option on all data observed. Tests were two-sided and significance was declared at a 5% threshold. Additionally, the cosmetic outcome score (full scale, from Poor to Excellent) 12 months after the last treatment and the improvement rate from the month-3 after the last treatment were descriptively presented by treatment.

RESULTS

Patient disposition and baseline characteristics

Out of the 234 screened patients, 196 had positive histology confirming sBCC diagnosis and were enrolled: 100 patients were randomised to MAL-PDT and 96 patients to surgery. Two thirds of the patients were males. The mean age was 63.8 years, ranging from 31 to 92 years. All patients were Caucasians. Baseline demographic characteristics were comparable in the two treatment groups (Table 1).

Kommentar [Zeina5]: This sentence was modified in order to precise the reason for non enrolment

On average in both groups, patients had 1.4 lesions. Most patients in each group had one lesion (79/100, 79% in the MAL PDT group and 77/96, 80.2% in the surgery group). In both groups, the majority of lesions were located on the trunk/neck. A slight unevenness could be observed between the two treatment groups in terms of lesion location. Indeed, there were slightly more lesions on the face/scalp in the MAL-PDT group than in the surgery group (Table 1).

Patient disposition is depicted in Figure 1. Overall, 173/196 patients (88.3%) completed the study. Few major deviations were observed. Fourteen patients (7.1%) were considered non eligible for the PP analysis. There were more patients with at least one major deviation in the surgery group than in the MAL-PDT group (10/96 [10.3%] vs. 4/100 [4.0%], respectively). The most frequent major protocol deviation was lack of post baseline data or lack of efficacy data at 3 months: 4/100 patients (4.0%) in the MAL-PDT group and 8/96 patients (8.3%) in the surgery group. The PP population included 182 patients (92.9%).

MAL-PDT procedure

Overall, about 90% of the lesions were prepared before cream application for the first cycle (baseline and week 1), and about 85% at the second cycle. The mean time of cream application was 3:05 hours with a mean illumination time necessary to deliver the required dose of 8:22 minutes. No patients needed to have illumination stopped and restarted due to pain at the first session of both cycles, and only 3% of the patients needed so at the second session of each cycle (4/133 patients at week 1 and 1/35 patient at week 14).

Surgery

After surgical resection, 8/125 specimens (6.4%) showed a histologically positive margin. For all of them, no further surgery was made and patients remained in the study as it is standard of care in sBCC.

Clinical lesion response

At 3 months, both treatments showed a high percentage reduction in lesion count by patient: 92.2% mean lesion count reduction with MAL-PDT versus 99.2% with surgery (PP population). The 95% C.I. lower limit of the difference between treatments was -12.1% confirming that MAL-PDT was non inferior to surgery (within the pre-specified margin of -15%). In terms of lesion response, 118/128 lesions (92.2%) showed complete clinical response at 3 months with MAL-PDT versus 117/118 (99.2%) with surgery (PP population). The observed results followed the same trend irrespective of lesion size or location except for lesions located on face/scalp which complete response rate was 100% in the MAL-PDT group (Table 2). The analysis on the ITT population confirmed the PP analysis.

Overall, 91/128 lesions (71.1%) had been treated with only one cycle of MAL-PDT, representing 76.3% (90/118) of the cleared lesions.

Among the lesions showing complete clinical response at 3 months, 9.3% of lesions (11/118) recurred at 12 months in the MAL-PDT group and none in the surgery group (0/117). See Table 3 for details per location.

Kommentar [Zeina6]:
This was initially in a separate paragraph. Entitled 'Recurrence rate'

Cosmetic outcome

Whether assessed by the investigators or by the patients, the cosmetic outcome of cleared lesions was statistically superior with MAL-PDT than with surgery at each visit after last treatment. At 12 months, per the investigator's assessment, 77/83 patients (92.8%) in the MAL-DT group vs. 44/86 (51.2%) of patients in the surgery group ($p < 0.001$) were considered "success", i.e. mean cosmetic outcome across lesions at least good.

The proportion of lesions showing excellent cosmetic outcome was much higher with MAL-PDT from 3 months, and it substantially improved with time in the MAL-PDT group whereas it

remained almost unchanged in the surgery group (Figure 2). No poor cosmetic outcome was observed with MAL-PDT at any visit, except for one lesion at 3 months per the patient's assessment.

An example of the outcomes of MAL-PDT and simple excision surgery is shown in Figure 3.

Adverse events

The incidence of treatment related adverse events (AEs) was higher in the MAL-PDT group than in the surgery group: in the MAL-PDT group, 37/100 patients (37%) reported 65 related AEs versus 14/96 patients (14.6%) with 21 related AEs in the surgery group. Related AEs that occurred in at least 2 patients are described in Table 4. Most related AEs were expected AEs of dermatological nature: photosensitivity reaction for MAL-PDT (31/100 patients [31%] with 57 AEs), and wound infection for surgery (5/96 patients [5.2%] with 5 AEs). All related AEs were of mild or moderate severity, except one severe wound infection reported in the surgery group.

Among the 37 patients with AEs related to MAL-PDT, only 4 (11%) required treatment for their AEs, mainly limited use of analgesic or antiseptic drugs, compared to 8 out of the 14 patients (57%) who reported AEs related to surgery necessitating mostly a 1 to 2-week course of systemic antibiotic therapy (5 patients) or repeated intake of analgesics (3 patients).

A total of 21 serious AEs were reported, none were considered as related to any of the 2 study procedures. AEs leading to permanent discontinuation of study occurred in 2 patients in the MAL-PDT group and in 1 in the surgery group. None of them were treatment-related.

DISCUSSION

In the treatment of sBCC, this is the only published study comparing topical PDT and simple excision surgery, commonly regarded as the treatment of choice in this indication. The present results demonstrate that 3 months after last treatment, the efficacy of MAL-PDT is comparable to that of surgery in the treatment of sBCC: 92.2% of lesions showed complete

Kommentar [Zeina7]: This section was re-ordered according to the following plan: (i) main results of efficacy (+ recurrence), cosmetic outcome and safety; (ii) limitations; (iii) advantages of MAL-PDT, i.e. excellent cosmetic outcome, mainly in areas where surgery is less appropriate

clinical response at 3 months with MAL-PDT versus 99.2% with surgery. However, at 12 months, 9.3% of lesions recurred with MAL-PDT compared to none with surgery.

Kommentar [Zeina8]:
Rephrased

Cosmetic outcome of lesions cleared at 12 months, whether assessed by the investigator or by the patient, was superior for MAL-PDT over surgery. Twelve months after last treatment, 93% of patients in the MAL-PDT group vs. 51% of patients in the surgery group had a mean cosmetic outcome across lesions scored at least 'good' by the investigator. Moreover, cosmetic outcome markedly improved with time in the MAL-PDT group, unlike surgery.

In the present study, although side effects observed with MAL-PDT (mainly photosensitivity reaction) were notably more frequent than with surgery (mainly wound infection), they were of mild to moderate intensity, transient and easily manageable: only 11% of patients required their side effects to be treated, and it was with a one-day treatment of analgesic or antiseptic drug, while 57% of patients with surgery-related adverse events needed treatment for this, in particular with systemic antibiotics. This issue had been previously described with surgery and also with cryotherapy.²⁵

Our study was limited to a 12-month follow-up where a longer period would have revealed a large number of relapses. However, previous findings on recurrence rates with MAL-PDT at 12 months^{24,26} are similar to the 9.3% rate obtained in our study and one might suggest that longer follow-up period would have led to recurrence rates comparable to those published²⁴. Moreover, it was shown that recurrences with MAL-PDT reach a plateau at 36 months dismissing the need for longer observation periods.

The open design of the present study might have constituted a bias. Indeed, though randomised treatment allocation was ensured with the system of randomisation cards, and with the record of date and time each card was disclosed, the lesion response evaluator could identify the allocated treatment modality based on the aspect of the residual wound. Moreover, it should be noted that eligible lesions were those considered suitable for simple

excision surgery. Therefore, lesions were excluded that were located on areas where MAL-PDT would have been the most appropriate treatment.

In our study, no histological confirmation of lesion response was required. Response to treatment was based on clinical evaluation only, reflecting real-life practice. Nevertheless, it is interesting to notice that no recurrence was observed among the 6.4% of lesions with histologically positive margins following excision.

The advantages conveyed by MAL-PDT in terms of cosmesis makes this therapeutic modality particularly suitable for the treatment of superficial BCC. Indeed, sBCC is a disease of relatively low risk and is more frequent in young patients¹⁴, and often located on areas prone to hypertrophic scarring and/or keloids such as the trunk and legs^{7,9}. In addition, as superficial BCCs are often more than 10 mm in diameter before they are diagnosed as such, because they first appear to be actinic keratoses or inflammatory lesions, their excision in areas likely to show poor healing may lead to scarring or disfigurement or require skin grafts, with potential significant psychological impact. This aspect is supported by a discrete-choice experiment conducted with members of the Australian general public, which found that patients are willing to pay for the better cosmetic outcomes provided by MAL-PDT rather than receive simple excision for BCC.²⁷ High clearance rates with superior cosmetic outcome obtained with MAL-PDT are also of great interest for the treatment of extensive and multiple lesions. In a previous study, it was found that cosmetic outcome improved over time in difficult-to-treat populations who might be expected to have poor cosmetic outcomes.²⁸

Another interesting feature with MAL-PDT is the ease of re-treatment in case of non complete response or recurrence: there is no long term or cumulative toxicity of MAL-PDT and no secondary defect or scarring.

In conclusion, in line with international recommendations on the use of PDT for nonmelanoma skin cancer¹⁴, the results of our study suggest that owing to its high efficacy and excellent

cosmetic outcome, MAL-PDT can be considered as an option to surgery in the treatment of superficial BCCs.

ACKNOWLEDGEMENTS

The authors would like to thank the following persons for their participation in this study: *From Australia:* P. Foley, Melbourne; A. Howard Footscray; R. Paver, Westmead - *From Germany:* J. P. Bauerschmitz, Erlangen; A. Hauschild, Kiel; H. Gollnick, Magdeburg; W. Klövekorn, Gilching; T. Lüger, Münster; M. Meurer, Dresden; M. Röcken, Tübingen; Y. Zimmer, Berlin - *From Switzerland:* L. Braathen, Bern – Barbara Lätsch, Zürich - *From the UK:* A. Abdullah, Birmingham; R. Azurdia, Liverpool – S. Campbell, Truro; S. Cliff, Crawley; D. Kemmet, Edinburgh; A. Kurwa, London; T. Ormerod, Aberdeen; L. Rhodes, Salford - and Zeina Saab (Galderma), medical writer, for editorial assistance.

REFERENCES

1. Lear W, Dahlke E, Murray CA. Basal cell carcinoma: review of epidemiology, pathogenesis, and associated risk factors. *J Cutan Med Surg*. 2007 Jan-Feb;11(1):19-30. Review.
2. Diepgen T.L., Mahler V., The epidemiology of skin cancer. *Br J. Dermatol*, 2002;145: p.1-6.
3. Marks R. Epidemiology of non-melanoma skin cancer and solar keratoses in Australia: a tale of self-immolation in Elysian fields. *Australas J Dermatol*. 1997 Jun;38 Suppl 1:S26-9. Review.
4. Skin Cancer. Non-melanoma Skin Cancer in the Mediterranean Area, a report by JG Estrada available at: <http://www.touchbriefings.com/pdf/2707/Estrada.pdf>. Accessed October 2, 2007.
5. Goldberg LH. Basal Cell Carcinoma. *Lancet* 1996;347:663-7
6. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. *Arch Dermatol*. 1997 May;133(5):593-6.
7. Bastiaens MT, Hoefnagel JJ, Bruijn JA, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinoma indicate different types of tumors. *J Invest Dermatol*. 1998 Jun;110(6):880-4.
8. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. *Br J Dermatol*. 2002 Jul;147(1):41-7.
9. Raasch BA, Buettner PG, Garbe C. Basal cell carcinoma: histological classification and body-site distribution. *Br J Dermatol*. 2006 Aug;155(2):401-7.

10. Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD003412. Review.
11. Ceilley RI, Del Rosso JQ. Current modalities and new advances in the treatment of basal cell carcinoma. *Int J Dermatol*. 2006 May;45(5):489-98. Review.
12. Kumar P, Orton CI, McWilliam LJ, Watson S. Incidence of incomplete excision in surgically treated basal cell carcinoma: a retrospective clinical audit. *Br J Plast Surg*. 2000 Oct;53(7):563-6.
13. Nagore E, Grau C, Molinero J, Fortea JM. Positive margins in basal cell carcinoma: relationship to clinical features and recurrence risk. A retrospective study of 248 patients. *J Eur Acad Dermatol Venereol*. 2003 Mar;17(2):167-70.
14. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, Roelandts R, Wennberg AM, Morton CA; International Society for Photodynamic Therapy in Dermatology. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *International Society for Photodynamic Therapy in Dermatology*, 2005. *J Am Acad Dermatol*. 2007 Jan;56(1):125-43.
15. Kormeili T, Yamauchi PS, Lowe NJ. Topical photodynamic therapy in clinical dermatology. *Br J Dermatol*. 2004 Jun;150(6):1061-9. Review.
16. Pariser DM, Lowe NJ, Stewart DM, Jarratt MT, Lucky AW, Pariser RJ, Yamauchi PS. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol*. 2003 Feb;48(2):227-32.
17. Tarstedt M, Rosdahl I, Berne B, Svanberg K, Wennberg AM. A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol*. 2005;85(5):424-8.

18. Morton C, Campbell S, Gupta G, Keohane S, Lear J, Zaki I, Walton S, Kerrouche N, Thomas G, Soto P; AKtion Investigators. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol*. 2006 Nov;155(5):1029-36.
19. Rhodes LE, de Rie M, Enstrom Y, Groves R, Morken T, Goulden V, Wong GA, Grob JJ, Varma S, Wolf P. Five-Year Follow-up of a Randomized, Prospective Trial of Topical Methyl Aminolevulinate Photodynamic Therapy vs Surgery for Nodular Basal Cell Carcinoma. *Arch Dermatol*. 2007;143:1131-6.
20. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol*. 2007 May;156(5):793-801.
21. Szeimies RM. Methyl aminolevulinate-photodynamic therapy for basal cell carcinoma. *Dermatol Clin*. 2007 Jan;25(1):89-94. Review.
22. Morton CA. Methyl aminolevulinate: actinic keratoses and Bowen's disease. *Dermatol Clin*. 2007 Jan;25(1):81-7. Review.
23. Foley P. Clinical efficacy of methyl aminolevulinate (Metvix) photodynamic therapy. *J Dermatolog Treat*. 2003;14 Suppl 3:15-22. Review.
24. Basset-Seguín N, Ibbotson S, Emtestam L, Tarstedt M. Photodynamic Therapy using Metvix is as efficacious as cryotherapy in BCC, with better cosmetic results. *J Eur Acad Dermatol Venereol*. 2004;18:412
25. Thissen MR, Nieman FH, Ideler AH, Berretty PJ, Neumann HA. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. *Dermatol Surg*. 2000 Aug;26(8):759-64.
26. Soler AM, Warloe T, Berner A, Giercksky KE. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas

Kommentar [Zeina9]:
Updated

treated with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *Br J Dermatol*. 2001 Sep;145(3):467-71.

27. Weston A, Fitzgerald P. Discrete choice experiment to derive willingness to pay for methyl aminolevulinate photodynamic therapy versus simple excision surgery in basal cell carcinoma. *Pharmacoeconomics*. 2004;22(18):1195-208.
28. Vinciullo C, Elliott T, Francis D, Gebauer K, Spelman L, Nguyen R, Weightman W, Sheridan A, Reid C, Czarnecki D, Murrell D. Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol*. 2005 Apr;152(4):765-72.

Table 1: Baseline patient demographics and lesion characteristics (ITT population)

		MAL-PDT (N = 100)	Surgery (N = 96)	Total (N = 196)
Gender				
	Male	n (%)	64 (64.0)	66 (68.8)
	Female		30 (31.3)	66 (33.7)
Age (years)	Mean \pm sd	64.5 \pm 12.7	63.1 \pm 13.9	63.8 \pm 13.3
	Range	33; 85	31; 92	31; 92
Race	Caucasian n (%)	100 (100)	96 (100)	196 (100)
Lesion number per patient	Mean \pm sd	1.4 \pm 0.8	1.4 \pm 0.9	-
	Min; Max	1; 5	1; 5	-
Lesion distribution	1 lesion n (%)	79 (79)	77 (80.2)	-
	\geq 1 lesion n (%)	21 (21)	19 (19.8)	-
Lesion diameter (mm) per patient	Mean \pm sd	12.5 \pm 3.7	12.6 \pm 3.7	-
Lesion location	Total	135	132	-
	Trunk/neck; n (%)	81 (60)	93 (70.5)	-
	Extremities; n (%)	39 (28.9%)	33 (25.0)	-
	Face/scalp; n (%)	15 (11.1%)	6 (4.5)	-

Table 2: Lesion complete response to treatment at 3 months (PP population)

	MAL-PDT	Surgery
Overall lesion response, N (%)	118 /128 (92.2)	117/118 (99.2)
Lesion response by location, N (%)		
Face/scalp	15/15 (100)	4/4 (100)
Trunk/neck	69/76 (90.8)	82/83 (98.8)
Extremities	34/37 (91.9)	31/31 (100)
Lesion response by size, N (%)		
7 – 14 mm	78/85 (91.8)	69/70 (98.6)
15 – 20 mm	40/43 (93.0)	43/43 (100)

Table 3: Lesion recurrence at 12 months (ITT population) by location

	MAL-PDT	Surgery
Cleared lesions, N (%)	107/118 (90.7)	117/117 (100)
Recurred lesions, N (%)	11/118 (9.3)	0/117 (0)
Face/scalp	4/15 (26.7)	-
Trunk/neck	3/69 (4.3)	-
Extremities	4/34 (11.8)	-

Table 4: Treatment related adverse events

	MAL-PDT N=100	Surgery N=96
Patients with related AEs, N(%)	37 (37)	14 (14.6)
Most common related AEs ^a , N(%)		
Photosensitivity reaction ^b	31 (31)	-
Wound infection	-	5 (5.2)
Erythema	-	3 (3.1)
Post procedural pain	-	3 (3.1)
Pain	2 (2)	1 (1)
Milia	2 (2)	-
Wound dehiscence	-	2 (2.1)

^aReported by at least 2 patients

^b *Photosensitivity reaction* included all expected reactions such as skin discomfort, burning sensation, erythema, stinging, among others, reported with MAL-PDT

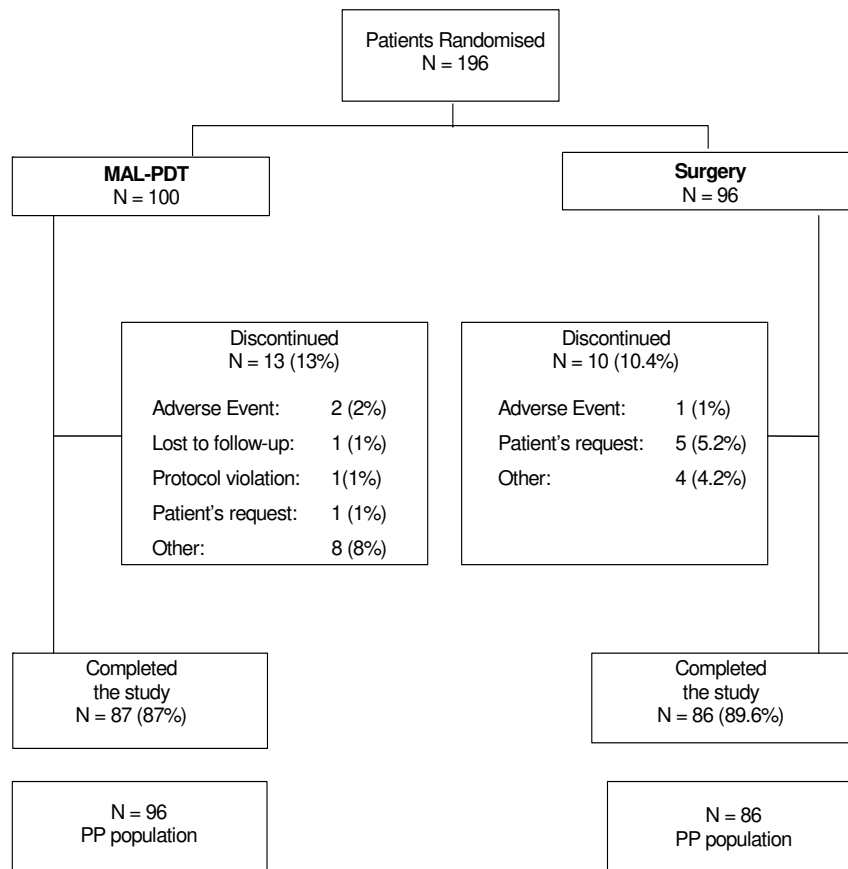
Figure 1: Patient disposition

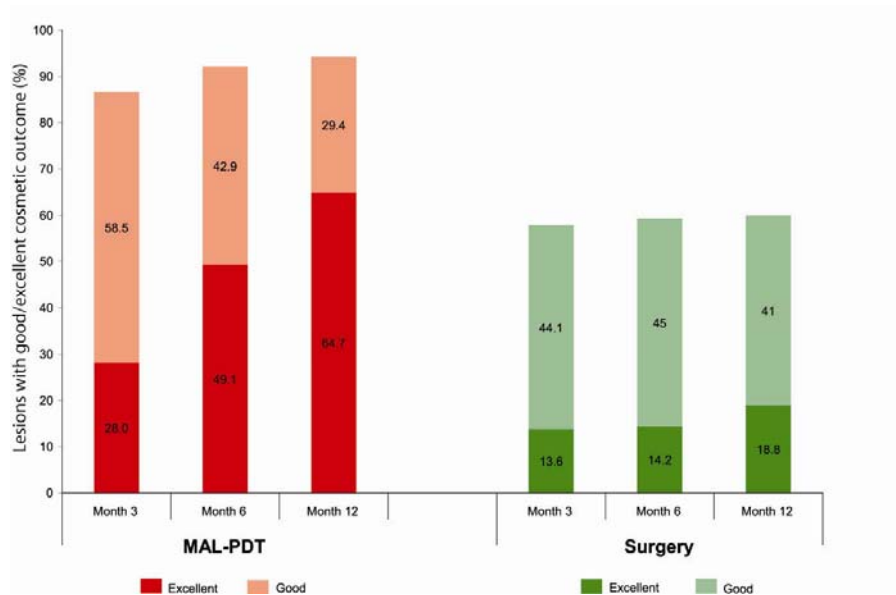
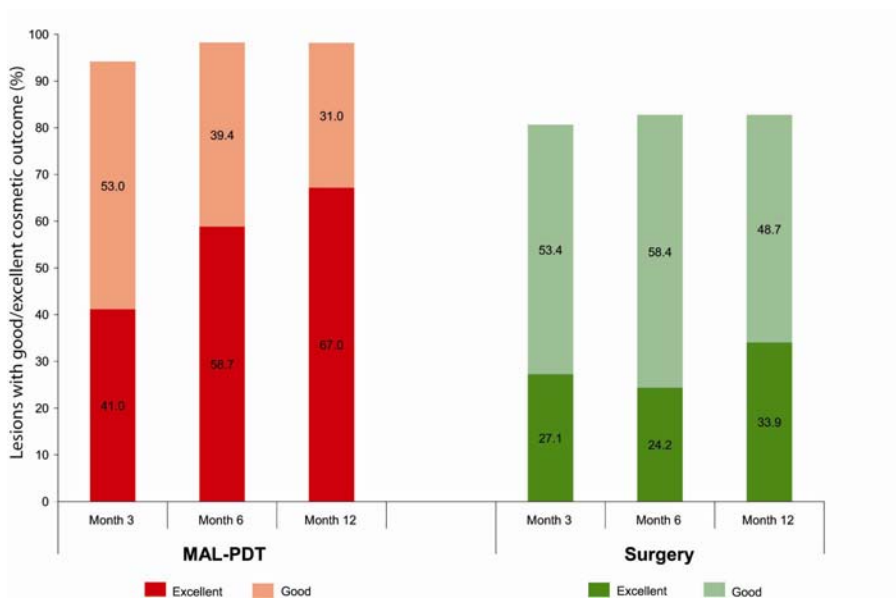
Figure 2: Excellent or good cosmetic outcome over time (observed cases)**a) as assessed by the investigator****b) as assessed by the patient**

Figure 3: Patient pictures

Lesion treated with one MAL-PDT cycle

Lesion treated with surgery

Before treatment

After 3 months

After 12 months